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EVENT-RELATED BRAIN POTENTIALS: AN ALTERNATIVE METHODOLOGY FOR NEUROTOXICOLOGICAL RESEARCH

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16. ABSTRACT

One of the problems encountered in studies of glue sniffing, and other types of solvent poisoning is addiction. This problem also afflicts researchers who tend to become addicted to a particular methodology. This paper will review some alternatives to the behavioral methods to which many of us have become addicted. These alternatives include sensory evoked potentials and event-related slow potentials of the brain. Evoked potentials are sensitive, clinically proven, indices of sensory deficits, while event-related slow potentials are sensitive, albeit experimental, indices of cognitive dysfunction. Evidence is accumulating that evoked and slow potential measures may also be sensitive indices of neurotoxic effect.

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One of the problems encountered in studies of glue sniffing, and other types of solvent poisoning is addiction. This problem also afflicts researchers who tend to become addicted to a particular methodology. This paper will review some alternatives to the behavioral methods to which many of us have become addicted. These alternatives include sensory evoked potentials and event-related slow potentials of the brain. Evoked potentials are sensitive, clinically proven, indices of sensory deficits, while event-related slow potentials are sensitive, albeit experimental, indices of cognitive dysfunction. Evidence is accumulating that evoked and slow potential measures may also be sensitive indices of neurotoxic effect (Otto, 1977; 1982a, 1982b; Otto and Reiter, 1978).

There are three types of clinically validated evoked potential measures that have straightforward application to neurotoxicity testing. The first is the brainstem auditory evoked potential (BAEP), one of the few evoked potential phenomena for which the neural origins have been relatively well established (see review by Rowe, 1981). A typical BAEP is illustrated in figure 1. The first wave is generated peripherally in the acoustic nerve, the second from the region of the cochlear nucleus, the third is associated with the superior olivary complex, the fourth with the lateral lemniscus, and the fifth with the inferior colliculus. The correlation between anatomy and phenomenology is sufficiently good that the neurologist can use the BAEP to assist in localizing lesions in the auditory

pathway and in diagnosing nonspecific demyelinating diseases such as multiple sclerosis (Starr, 1977). Since neurotoxicants tend to produce symmetrical, diffuse effects on CNS function (Schaumberg et al, 1981) similar to multiple sclerosis, BAEPs should provide a sensitive index of neurotoxicity -- particularly in the case of chemicals that produce demyelinating effects.

Several other features of the BAEP suggest its utility in toxicity testing. First, the BAEP is not affected by changes in attentional state. As long as the auditory pathway is intact, anesthesia does not alter BAEP latencies (Starr, 1977). Secondly, the measure is immune to cultural bias since no verbal mediation is required. In addition, BAEPs are simple to record and the latency measures are easy to make and interpret. Central conduction time in the auditory pathway can be determined by subtracting the latency of wave I (acoustic nerve) from wave V (region of the inferior colliculus).

The second measure that I would add to a neurotoxicity test battery is the pattern reversal visual evoked potential (PREP). In this test, dark and light squares of a checkerboard pattern are reversed repetitively on a video display. This measure has been found to be more effective than the traditional flash visual evoked response in the diagnosis of multiple sclerosis (Halliday et al, 1973). PREP waveforms elicited by stimulating the left and right eyes of a patient with multiple sclerosis are shown in figure 2. The left-right imbalance, indexed by a differential latency of about 14 msecs in the P100 component, is clinically abnormal and, in this case, diagnostic of multiple sclerosis (Stockard et al, 1979).

The flash evoked potential has been used widely for toxicity testing in animal models (cf. Fox et al, 1977; Dyer et al, 1979; Cooper et al, 1980). For many substances, it seems to be a useful measure. In view of the lack of sensitivity in the clinical population of the flash evoked response, the PREP appears to be a better candidate for human neurotoxicity testing. Several Institutes of Occupational Medicine (Baltimore, Helsinki, Stockholm) have begun to use the PREP in the neurobehavioral assessment of workers, but no definitive data from these studies are yet available (see Elofsson et al, 1980).

The two measures described above have other characteristics that make them useful for neurotoxicity testing purposes. Both the BAEP (Hecox and Galambos, 1974) and PREP (Sokol and Jones, 1979) reach mature latency values by 18 months of age and remain relatively constant throughout adult life, although there may be a slight slowing in latencies in the elderly. In general, these measures are very robust and very reliable.

The third electrophysiological measure that I would suggest using in a neurotoxicity test battery is the somatosensory evoked potential (SEP). Anatomically the somatosensory system is ideal for human neurotoxicity testing because the long peripheral nerves are accessible for measurement at many points along the sensory pathway. By stimulating a distal point in the pathway, both peripheral and central nerve conduction measures can be obtained simultaneously as shown in figure 3. Peripheral nerve conduction velocity is determined by measuring between two points on the peripheral nerve. Central conduction time is calculated by subtracting the arrival time of the afferent volley at the dorsal column nucleus (N14 latency)

from the arrival time in the postcentral gyrus (N20 latency). This method can be used in neurotoxicological assessment to determine if a deficit is peripheral or central (cf. Eisen and Odusote, 1980). Other SEP measures have been found to indicate neurological disorders in the spinal cord, brainstem and thalamus (Noel and Desmedt, 1980).

Few attempts have been made to apply SEPs in human neurotoxicity testing. Seppalainen (1978) reported preliminary evidence that the scalp-recorded SEP was more sensitive than peripheral nerve conduction measures of subclinical neuropathy in lead-exposed workers. Groll-Knapp et al (1978) compared the effects of 100 ppm (5.5% COHb) and 200 ppm (9.7% COHb) CO exposure on auditory, visual and somatosensory evoked potentials. SEP amplitude was significantly reduced at both exposure levels, while auditory and visual EPs were unchanged. Zappoli et al (1978), on the other hand, did not find the SEP useful in diagnosing toxic polyneuropathy of workers exposed to industrial adhesive solvents.

The three measures described above are clinically validated. There are other electrophysiological measures with possible applications in toxicological research that must be considered experimental because the tests have not been standardized and population norms are not available. I am referring here to event-related slow brain potentials (ERSP). Sensory evoked potentials measure the integrity of sensory pathways, but provide no information on cortical integration. In contrast, ERSPs are usually recorded in the context of a behavioral task and thus reflect the integration of sensory input and motor output. For example, the subject may be presented with a single digit once per second and asked to press a button each time he detects a run of three odd or three even

numbers. An example of ERSPs elicited in this type of continuous performance task is shown in figure 4. The solid line represents correct rejection trials where the first two digits in the string were the same, but the third digit differed (e.g., 3-3-8). In these trials the subject correctly refrained from pressing the button. Following the third stimulus a component (called the P300 wave) appeared in the trace indicating that a correct no-response decision had been made. The dashed line represents a set of miss trials, where the individual failed to detect a target string of three identical digits. In this trace, the P300 component was absent. Note that the subject refrained from button pressing in both sets of trials, but the P300 wave occurred only when a correct no-response decision was made. The P300 wave thus constitutes a robust, easily recordable index of information processing in the brain, a convenient noninvasive measure of cognitive function.

P300 amplitude and latency have been studied extensively by psychophysiologists and related to a variety of cognitive functions including selective attention, response set, decision-making, signal detection, orienting, and uncertainty (cf. Tueting, 1978). As yet, however, the clinical relevance of this waveform remains to be demonstrated in a convincing manner. The lack of knowledge of the neuroanatomical, neurophysiological, and neurochemical substrates of the P300 limit clinical applications. Otto et al (1978) failed to find any relationship between P300 amplitude and carboxyhemoglobin levels in young adults, but no systematic effort has been made to explore the utility of the P300 in neurotoxicology.

Another extensively studied ERSP is the contingent negative variation (CNV) first described by Walter et al (1964). CNV is a slow negative shift in EEG baseline that occurs between the warning and imperative stimuli in a fixed foreperiod reaction time task. The CNV has also been related to a host of psychological variables including expectancy, motor preparation, attention/arousal, and concentration. Groll-Knapp et al (1972) reported that CNV amplitude and vigilance performance varied inversely with carbon monoxide exposure levels, although Groll-Knapp et al (1978) were unable to replicate earlier findings. Otto et al (1978) reported a paradoxical increase in CNV amplitude in subjects exposed to 100 ppm CO, but a decrease in subjects exposed to 200 ppm CO. Zappoli et al (1978) did not observe any effects of adhesive solvent exposure on CNV amplitude in shoe workers, despite EEG abnormalities indicative of diffuse brain damage in all subjects.

The most encouraging evidence of the potential utility of ERSPs in neurotoxicity testing derives from recent studies of slow cortical potentials in children with elevated body lead burden (Otto et al, 1981; 1982). A linear relationship between slow wave (SW) voltage and blood lead (PbB) level was observed in young children during sensory conditioning (Fig. 5). This effect was observed across a range of 6-55 µg/dl with no evidence of any threshold effect level. The only other biological parameter previously shown to be affected at such low PbB levels is delta-aminolevulinic acid dehydratase (Hernberg et al, 1970), a measure of heme synthesis. A similar linear relationship of SW voltage and PbB levels was observed in a subset of the children evaluated two years later when PbB levels were significantly reduced (Otto et al, 1982). Although the functional and

clinical significance of these data is not clearly understood, the results suggest that SW voltage is very sensitive to body lead burden in children.

With the exception of the pediatric lead data, the utility of ERSPs in neurotoxicological research has not been demonstrated convincingly. The problems which limit the clinical application of the P300, noted above, pertain also to the CNV and other ERSP measures. Methodological difficulties further limit the application of ERSP measures in clinical and neurotoxicological research. Eye and body movements produce considerable artifact during recording. Trials in which eye or body movements occur must be rejected from signal averages. Eye fixation on a visual target is usually required to minimize eye movement artifact. The complexity and expense of computerized data acquisition and analysis systems also limit the application of ERSP methods.

In conclusion, clinically validated sensory evoked potentials appear to be excellent candidates for human neurotoxicity testing. Event-related slow potentials, however, require standardization, validation, and technological simplification before these measures are likely to provide an effective antidote for our addiction to more traditional behavioral testing methods.

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FIGURE LEGENDS

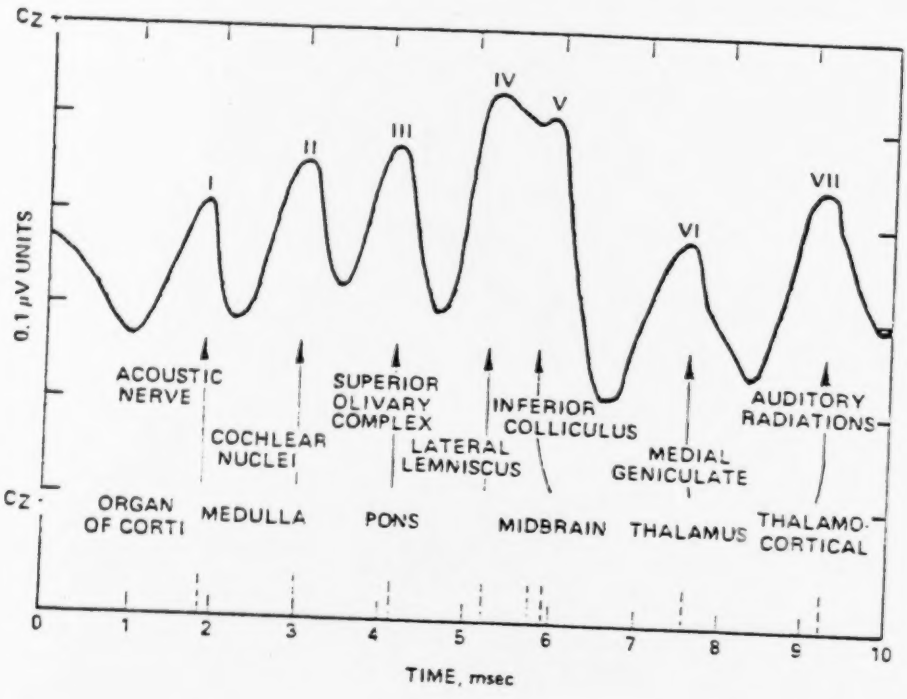
Fig. 1. Schematic drawing of the brainstem auditory evoked potential (BAEP) in an adult. Regions of the brain where each component originates are designated below the waveform.

Fig. 2. Pattern-reversal visual evoked potential (PREP) elicited by stimulating left and right eyes of a multiple sclerosis patient. Abnormal P100 latency is manifest in this case by interocular asymmetry rather than absolute latency prolongation. The longer latency in the right eye indicates subclinical right optic neuritis despite normal vision and ophthalmologic exam. (Adapted from Stockard et al, 1979, p. 194.)

Fig. 3. Procedure to derive central and peripheral conduction times in somatosensory pathways following median nerve stimulation. Peripheral conduction time is measured as the latency of the Erb's point potential. Central conduction time is measured as the latency difference between the N20 peak (cortex) and N14 peak (neck). (Adapted from Eisen and Odusote, 1980).

Fig. 4. Summary averages of correct rejection (CR) and miss trials of seven subjects during a continuous performance task. Note that the P300 component is present in CR trials, but absent in miss trials.

Fig. 5. Dose-response relationship of slow wave (SW) voltage and blood lead (PbB) levels in young children during sensory conditioning. SW voltage varied linearly with PbB, but the slope of this function changed with age. Predicted SW voltage and 95% confidence bounds are depicted in 13 and 75 month old children as a function of PbB. (Adapted from Otto et al, 1981, p. 235).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MEDIAL GENICULATE
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Fig. 1

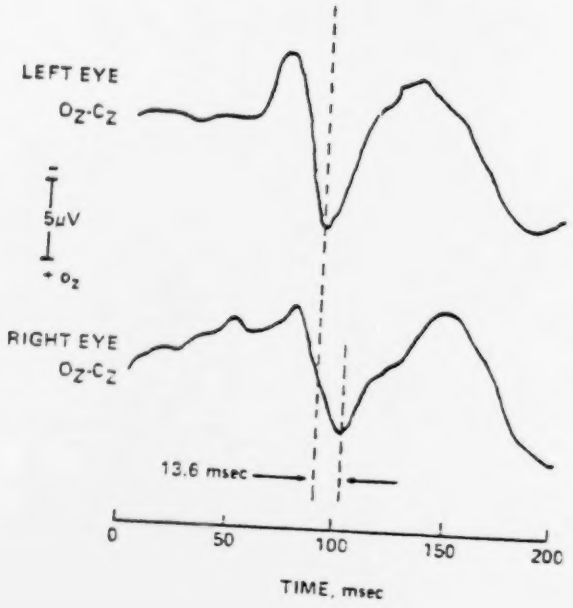
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Fig. 2

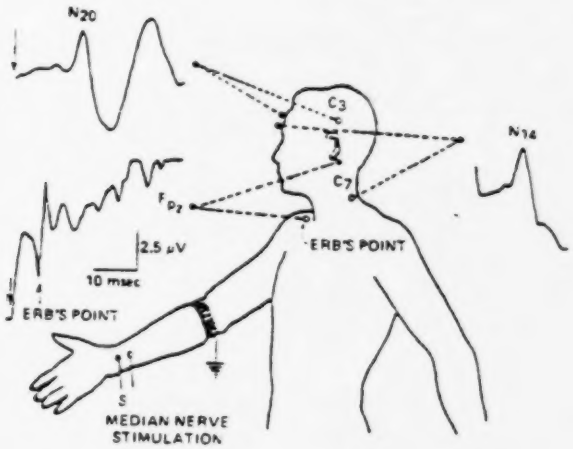
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Fig. 3

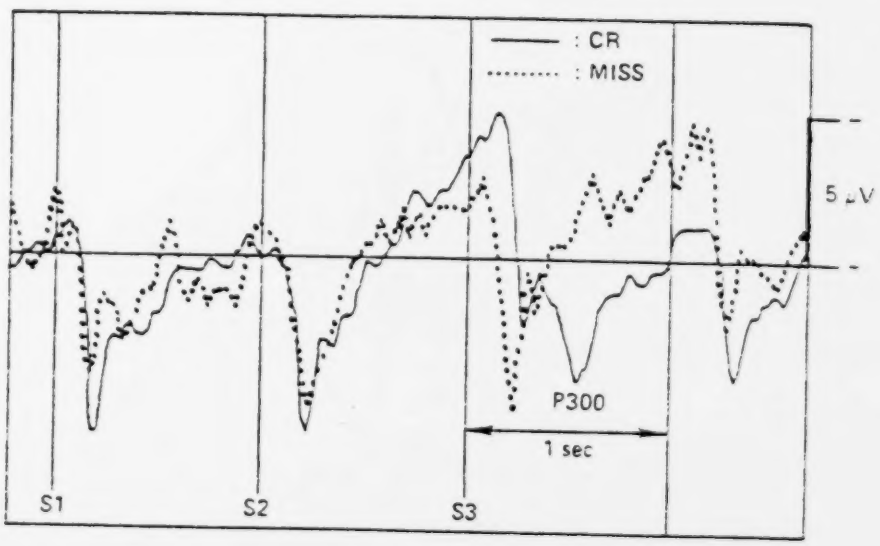
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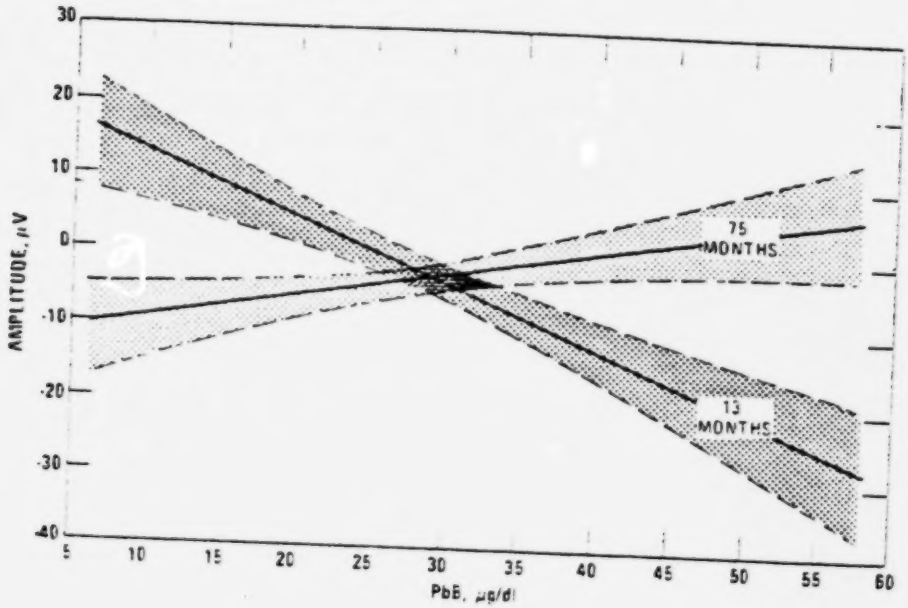
Fig. 4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PbB, μg/dl

Fig 5